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Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20857

CITIZEN PETITION

The undersigned submits this petition under section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(2)(C)), which authority has been delegated to the Commissioner of Food and Drugs under 21 C.F.R. § 5.10. Petitioner requests the Commissioner of Food and Drugs to declare that abbreviated new drug applications (ANDA) may be submitted for combination oxycodone hydrochloride/acetaminophen tablet products in strengths hereinafter described.

A. Action Requested

King & Spalding requests that the Commissioner declare that ANDAs may be submitted for combination oxycodone hydrochloride/acetaminophen tablet products in strengths of 2.5 mg/400 mg; 5.0 mg/400 mg; 7.5 mg/400 mg; and 10.0 mg/400 mg.

B. Statement of Grounds

Pain management has received considerable attention in the medical community in recent years. Pain management guidelines published by the Agency for Health Care Policy and Research (AHCPR) acknowledge the common "undertreatment" of pain. *See* Acute Pain Management Guideline Panel. *Acute Pain Management: Operative or Medical Procedures and Trauma. Clinical Practice Guideline.* AHCPR Pub. No. 92-0032. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services. Feb. 1992; Jacox A, Carr DB, Payne R, et. al. *Management of Cancer Pain. Clinical Practice Guideline* No. 9. AHCPR Pub. No. 94-0592. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services. March 1994. As a result of the recommendations contained in these guidelines, physicians have become more aggressive in treating pain.

AHCPR and other current guidelines for the management of both acute and chronic pain recommend extensive reliance on oral opioids in combination with non-opioid analgesics (i.e., NSAIDs and acetaminophen). The objective of such combination therapy is to allow appropriate

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dosage titration of the opioid (e.g., oxycodone) while administering a safe and effective dose of the non-opioid (e.g., acetaminophen). The dose of the opioid needed is dependent upon the severity of the pain being treated, the degree of tolerance that the patient may have developed, as well as the individual characteristics of the patient such as weight, age, diagnosis, and general medical condition. The daily dose of acetaminophen must not exceed 4000 mg per day to avoid the risk of hepatotoxicity, and many doctors prefer to prescribe a lower daily dose of acetaminophen.

The reference listed drugs upon which this petition is based are Endo Pharmaceuticals' oxycodone hydrochloride/acetaminophen products in the following strengths: 2.5 mg/325 mg; 5.0 mg/325 mg; 7.5 mg/500 mg; and 10.0 mg/650 mg. The approved labeling for these products states:

> Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of opioids . . . . The usual adult dosage is one tablet every 6 hours as needed for pain. The total daily dose of acetaminophen should not exceed 4 grams.

The addition of these four proposed formulations containing 2.5 mg oxycodone hydrochloride/400 mg acetaminophen; 5.0 mg oxycodone hydrochloride/400 mg acetaminophen; 7.5 mg oxycodone hydrochloride/400 mg acetaminophen and 10 mg oxycodone hydrochloride/400 mg acetaminophen will make it possible for doctors to individualize the dose of oxycodone while maintaining a safe level of acetaminophen. In order for the patient not to exceed the recommended daily dose of acetaminophen, the patient should not take more than ten tablets per day.

AHCPR emphasizes that in using medication to manage pain, the doctor must individualize the regimen to the patient. The addition of these formulations will facilitate the physician's titrating the appropriate dose of oxycodone and acetaminophen against the patient's severity of pain and that patient's response, reserving the higher dose formulations for those patients with more severe pain or those who have become tolerant to opioids. The 7.5 mg and 10.0 mg doses of oxycodone hydrochloride are combined with lower doses of acetaminophen than is contained in the higher oxycodone hydrochloride doses of the reference drugs (500 mg and 600 mg), thus reducing the risk of acetaminophen hepatotoxicity when more pain relief is needed.

Investigations are unnecessary to show the safety and effectiveness of these proposed dosage strengths. The safety of oxycodone combined with acetaminophen is well established through over twenty years of use. Adverse events associated with this combination are well

known and are those characteristic of oxycodone and other oral opioids and acetaminophen. The safe maximum daily dose of most opioid/acetaminophen combinations is determined not by the opioid component but rather by the need to limit the dose of acetaminophen to 4000 mg/day.

Oxycodone by itself is currently marketed in approved strengths ranging from 5 mg per tablet to 20 mg/ml solution (e.g., Percolone® 5 mg tablet, M-oxy® 5 mg tablet, Roxicodone® 5 mg tablet and 20 mg/ml oral solution). These products have approved dosage recommendations for adults of 10 mg to 30 mg of oxycodone every four hours as needed with no upper limit on daily dosage being stated.

AHCPR clinical practice guidelines recommend usual starting doses of oxycodone of 10 mg q 3-4 hr for moderate to severe pain, *see id.*, and the American Pain Society's guidelines on Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain recommend a starting dose for oxycodone of 5 mg for mild to moderate pain and 15 to 30 mg for severe pain. American Pain Society, *Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain* (4th ed. 1999).

The proposed acetaminophen dose of 400 mg is recognized as safe and effective both as a single entity and as a constituent of opioid combination analgesics. Acetaminophen purchased over-the-counter is recognized as safe and effective for adults at doses from 325 mg to a maximum single dose of 1000 mg. *See* 53 Fed. Reg. 46204 (1988). With the exception of patients who abuse alcohol or who suffer hepatic dysfunction, daily doses of up to 4000 mg are generally accepted to be safe. *See id.*

The labeling for the proposed formulations is the same as the current approved labeling for the reference listed drugs with the variations permitted in 21 C.F.R. 314.94(a)(8)(iv). If a physician prescribes more than 10 tablets per day of the proposed combinations, the total daily dose of acetaminophen would exceed that accepted to be safe. Therefore, the labeling of the proposed products will contain the following safety statement: "The total daily dose of acetaminophen should not exceed four grams."

Draft labeling for the proposed products is included as Exhibit A. To avoid confusion, each product will be named as follows: "[TRADENAME] (Oxycodone and Acetaminophen Tablets, USP) [oxycodone hydrochloride/acetaminophen strength]." Side-by-side comparisons of the labeling for the reference listed drugs and the proposed drug products are included as Exhibit B.

C. Environmental Impact

As provided in 21 C.F.R. § 25.31, neither an environmental assessment nor an environmental impact statement is required.

D. Economic Impact

As provided in 21 C.F.R. § 10.30(b), economic impact information is to be submitted only when requested by the Commissioner following review of the petition.

E. Certification

The undersigned certifies, that to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petition which are unfavorable to the petition.

Jess H. Stribling

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Attachments